

AHRQ Healthcare Horizon Scanning System – Potential High-Impact Interventions Report

Priority Area 07: Diabetes Mellitus

Prepared for:

Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
5600 Fishers Lane
Rockville, MD 20857
www.ahrq.gov

Contract No. HHSA290-2010-00006-C

Prepared by:

ECRI Institute
5200 Butler Pike
Plymouth Meeting, PA 19462

December 2015

Statement of Funding and Purpose

This report incorporates data collected during implementation of the Agency for Healthcare Research and Quality (AHRQ) Healthcare Horizon Scanning System by ECRI Institute under contract to AHRQ, Rockville, MD (Contract No. HHSA290-2010-00006-C). The findings and conclusions in this document are those of the authors, who are responsible for its content, and do not necessarily represent the views of AHRQ. No statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

This report's content should not be construed as either endorsements or rejections of specific interventions. As topics are entered into the System, individual topic profiles are developed for technologies and programs that appear to be close to diffusion into practice in the United States. Those reports are sent to various experts with clinical, health systems, health administration, and/or research backgrounds for comment and opinions about potential for impact. The comments and opinions received are then considered and synthesized by ECRI Institute to identify interventions that experts deemed, through the comment process, to have potential for high impact. Please see the methods section for more details about this process. This report is produced twice annually and topics included may change depending on expert comments received on interventions issued for comment during the preceding 6 months.

A representative from AHRQ served as a Contracting Officer's Technical Representative and provided input during the implementation of the horizon scanning system. AHRQ did not directly participate in horizon scanning, assessing the leads for topics, or providing opinions regarding potential impact of interventions.

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Suggested citation: ECRI Institute. AHRQ Healthcare Horizon Scanning System Potential High-Impact Interventions: Priority Area 07: Diabetes Mellitus. (Prepared by ECRI Institute under Contract No. HHSA290-2010-00006-C.) Rockville, MD: Agency for Healthcare Research and Quality. December 2015. <http://effectivehealthcare.ahrq.gov/index.cfm/>

Preface

The purpose of the AHRQ Healthcare Horizon Scanning System is to conduct horizon scanning of emerging health care technologies and innovations to better inform patient-centered outcomes research investments at AHRQ through the Effective Health Care Program. The Healthcare Horizon Scanning System provides AHRQ a systematic process to identify and monitor emerging technologies and innovations in health care and to create an inventory of interventions that have the highest potential for impact on clinical care, the health care system, patient outcomes, and costs. It will also be a tool for the public to identify and find information on new health care technologies and interventions. Any investigator or funder of research will be able to use the AHRQ Healthcare Horizon Scanning System to select potential topics for research.

The health care technologies and innovations of interest for horizon scanning are those that have yet to diffuse into or become part of established health care practice. These health care interventions are still in the early stages of development or adoption, except in the case of new applications of already-diffused technologies. Consistent with the definitions of health care interventions provided by the National Academy of Medicine (formerly the Institute of Medicine) and the Federal Coordinating Council for Comparative Effectiveness Research, AHRQ is interested in innovations in drugs and biologics, medical devices, screening and diagnostic tests, procedures, services and programs, and care delivery.

Horizon scanning involves two processes. The first is identifying and monitoring new and evolving health care interventions that are purported to or may hold potential to diagnose, treat, or otherwise manage a particular condition or to improve care delivery for a variety of conditions. The second is analyzing the relevant health care context in which these new and evolving interventions exist to understand their potential impact on clinical care, the health care system, patient outcomes, and costs. It is NOT the goal of the AHRQ Healthcare Horizon Scanning System to make predictions on the future use and costs of any health care technology. Rather, the reports will help to inform and guide the planning and prioritization of research resources.

We welcome comments on this Potential High-Impact Interventions report. Send comments by mail to the Task Order Officer named in this report to: Agency for Healthcare Research and Quality, 5600 Fishers Lane, Rockville, MD 20857, or by email to: effectivehealthcare@ahrq.hhs.gov.

Richard Kronick, Ph.D.
Director
Agency for Healthcare Research and Quality

Arlene S. Bierman, M.D., M.S.
Director
Center for Evidence and Practice Improvement
Agency for Healthcare Research and Quality

Stephanie Chang, M.D., M.P.H.
Director, Evidence-based Practice Center Program
Center for Evidence and Practice Improvement
Agency for Healthcare Research and Quality

Elise Berliner, Ph.D.
Task Order Officer
Center for Evidence and Practice Improvement
Agency for Healthcare Research and Quality

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Executive Summary

Background

Horizon scanning is an activity undertaken to identify technological and system innovations that could have important impacts or bring about paradigm shifts. In the health care sector, horizon scanning pertains to identification of new (and new uses of existing) pharmaceuticals, medical devices, diagnostic tests and procedures, therapeutic interventions, rehabilitative interventions, behavioral health interventions, and public health and health promotion activities. In early 2010, the Agency for Healthcare Research and Quality (AHRQ) identified the need to establish a national Healthcare Horizon Scanning System to generate information to inform comparative-effectiveness research investments by AHRQ and other interested entities. AHRQ makes those investments in 14 priority areas. For purposes of horizon scanning, AHRQ's interests are broad and encompass drugs, devices, procedures, treatments, screening and diagnostics, therapeutics, surgery, programs, and care delivery innovations that address unmet needs. Thus, we refer to topics identified and tracked in the AHRQ Healthcare Horizon Scanning System generically as "interventions." The AHRQ Healthcare Horizon Scanning System implementation of a systematic horizon scanning protocol (developed between September 1 and November 30, 2010) began on December 1, 2010. The system is intended to identify interventions that purport to address an unmet need and are up to 3 years out on the horizon and then to follow them up to 2 years after initial entry into the health care system. Since that implementation, review of more than 24,500 leads about potential topics has resulted in identification and tracking of about 2,400 topics across the 14 AHRQ priority areas and 1 cross-cutting area; more than 750 topics are being actively tracked in the system.

Methods

As part of the Healthcare Horizon Scanning System activity, a report on interventions deemed as having potential for high impact on some aspect of health care or the health care system (e.g., patient outcomes, utilization, infrastructure, costs) is aggregated twice a year. Topics eligible for inclusion are those interventions expected to be within 0–3 years of potential diffusion (e.g., in phase III trials or for which some preliminary efficacy data in the target population are available) in the United States or that have just begun diffusing and that have completed an expert feedback loop.

The determination of impact is made using a systematic process that involves compiling information on topics and issuing topic drafts to a small group of various experts (selected topic by topic) to gather their opinions and impressions about potential impact. Those impressions are used to determine potential impact. Information is compiled for expert comment on topics at a granular level (i.e., similar drugs in the same class are read separately), and then topics in the same class of a device, drug, or biologic are aggregated for discussion and impact assessment at a class level for this report. The process uses a topic-specific structured form with text boxes for comments and a scoring system (1 minimal to 4 high) for potential impact in seven parameters. Participants are required to respond to all parameters.

The scores and opinions are then synthesized to discern those topics deemed by experts to have potential for high impact in one or more of the parameters. Experts are drawn from an expanding database ECRI Institute maintains of approximately 195 experts nationwide who were invited and agreed to participate. The experts comprise a range of generalists and specialists in the health care sector whose experience reflects clinical practice, clinical research, health care delivery, health business, health technology assessment, or health facility administration perspectives. Each expert uses the structured form to also disclose any potential intellectual or financial conflicts of interest

(COIs). Perspectives of an expert with a COI are balanced by perspectives of experts without COIs. No more than two experts with a possible COI are considered out of a total of the five to eight experts who are sought to provide comment for each topic. Experts are identified in the system by the perspective they bring (e.g., clinical, research, health systems, health business, health administration, health policy).

The topics included in this report had scores *and/or* supporting rationales at or above the overall average for all topics in this priority area that received comments by experts. Of key importance is that topic scores alone are not the sole criterion for inclusion—experts’ rationales are the main drivers for the designation of potentially high impact. We then associated topics that emerged as having potentially high impact with a further subcategorization of “lower,” “moderate,” or “higher” within the high-impact-potential range. As the Healthcare Horizon Scanning System grows in number of topics on which expert opinions are received and as the development status of the interventions changes, the list of topics designated as having potentially high impact is expected to change over time. This report is being generated twice a year.

For additional details on methods, please refer to the full AHRQ Healthcare Horizon Scanning System Protocol and Operations Manual published on AHRQ’s Effective Health Care Web site.

Results

The table below lists the four topics for which (1) preliminary phase III data for drugs, phase II (or equivalent) data for devices and procedures, or some human data for off-label uses or programs were available; (2) information was compiled before November 6, 2015, in this priority area; *and* (3) we received six to eight sets of comments from experts between January 1, 2015, and November 16, 2015. (Seventeen topics in this priority area were being tracked in the system as of November 6, 2015.) All four topics emerged as having high-impact potential on the basis of experts’ comments and assessment of potential impact, and we present summaries below. The material on interventions in this Executive Summary and report is organized alphabetically by disease state and then by intervention. Readers are encouraged to read the detailed information on each intervention that follows the Executive Summary.

Priority Area 07: Diabetes

Topic	High-Impact Potential
1. Exenatide continuous subcutaneous delivery (ITCA 650) for treatment of type 2 diabetes	Lower end of the high-impact-potential range
2. Fluocinolone acetonide implant (Iluvien) for treatment of diabetic macular edema	Lower end of the high-impact-potential range
3. Metabolic surgery for treatment of type 2 diabetes mellitus regardless of patient BMI	High
4. Ultra-rapid acting inhaled insulin (Technosphere insulin inhalation system with Afrezza) for treating diabetes that requires insulin	Lower end of the high-impact-potential range

Discussion

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia (elevated blood sugar). Diabetes-associated hyperglycemia results from dysfunction in either insulin secretion or insulin action or both. Most diabetes mellitus cases are either type 1 diabetes mellitus (T1DM; 5% of cases) or type 2 diabetes mellitus (T2DM; about 95% of cases). The American Diabetes Association (ADA) reports that in 2012 (the most recent year for which statistics are available), about 29 million children and adults in the United States had diabetes mellitus, but only about 21 million received a formal diagnosis. Furthermore, about 86 million people in the United States have

prediabetes or are at risk of developing T2DM. ADA stated that clinicians diagnose about 1.4 million new cases of diabetes each year in the United States in people aged 20 years or older.

T1DM risk factors include family history of T1DM and presence of certain genetics, whereas T2DM risk factors include being overweight, having a body that primarily stores fat in the abdomen, having a family history of the disease, or having another form of diabetes mellitus such as prediabetes or gestational diabetes. Being African American, American Indian, Asian American, or Hispanic is also a risk factor for T2DM. According to the U.S. Centers for Disease Control and Prevention, diagnosed T2DM is seven times as prevalent in adults aged 65 years or older as in adults aged 20–44 years.

ADA states that T1DM is caused by destruction of pancreatic beta cells, preventing secretion of insulin, and that this destruction is either immune mediated or idiopathic, with immune-mediated destruction accounting for the majority of cases. T1DM can occur at any age, but is most often diagnosed in children, adolescents, or young adults. Patients with T1DM require insulin therapy.

In T2DM, hyperglycemia is a result of insulin resistance or a diminished response to insulin. ADA states that patients with T2DM also often have a relative insulin deficiency and may have an insulin secretory defect in conjunction with insulin resistance.

Clinicians use one of three tests to diagnose diabetes mellitus: fasting plasma glucose test, oral glucose tolerance test, and casual plasma glucose level measurement. A fasting plasma glucose level of 126 mg/dL or more, an oral glucose tolerance test reading of 200 mg/dL or more, or a casual plasma glucose level of 200 mg/dL or more in conjunction with hyperglycemia symptoms all signal a diabetes diagnosis.

Additionally, physicians may order a glycated hemoglobin (HbA_{1c}) test. This test indicates the patient's average blood sugar level for the previous 2 or 3 months, and an HbA_{1c} level of 6.5% or higher on 2 separate tests is considered to be diagnostic of diabetes. HbA_{1c} levels ranging from 5.7% to 6.4% indicate a diagnosis of prediabetes, with normal levels below 5.7%.

Treating and managing diabetes to prevent complications require patients to make a lifelong commitment to exercising regularly, maintaining a healthy weight, eating healthy foods, monitoring blood sugar, and, in some cases, taking insulin. The primary treatment goal is to maintain blood sugar levels as close to normal as possible to delay or prevent complications.

After diagnosis and disease-type classification, patients undergo evaluation to detect complications, review glycemic control challenges, and establish treatment goals and a treatment plan. Clinicians generally encourage patients to achieve an HbA_{1c} level of 7% or lower because this value has been shown to reduce diabetes-associated microvascular complications. However, targets are individualized according to clinician judgment about the optimal goal for a specific patient.

For T2DM, several self-administered, oral antidiabetes agents, alone or in combination, are generally tried as first-line therapy. These include biguanides, sulfonylureas, alpha-glucosidase inhibitors, insulin sensitizers, insulin secretagogues, and dipeptidyl peptidase-4 (DPP-4) inhibitors. Many patients with T2DM do not meet treatment goals and require additional therapy with one of two types of injected antidiabetes agents: subcutaneous insulin or a glucagon-like peptide-1 (GLP-1) receptor agonist. Insulin supplementation has become increasingly common with T2DM.

Most interventions in development for diabetes focus on delaying disease onset in at-risk patients, improving diabetes management and treatment adherence, and for T1DM, developing options that prevent the body's autoimmune reaction against pancreatic islet cells or mimic the natural function of the pancreas to produce insulin. Some emerging technologies, such as the Iluvien[®] implant, target treatment of serious complications of diabetes, such as diabetic macular edema (DME). The American Academy of Ophthalmology (AAO) defines DME as swelling or thickening of the macula, a thin layer of light-sensitive tissue that lines the back of the eye and is responsible for detailed central vision. Macular edema develops when blood vessels in the retina

leak, causing the macula to swell and impairing its function. AAO states that DME is the most common form of vision loss for people with diabetes, particularly if left untreated.

Prior Potential High Impact Topics Archived

- **Insulin pump integrated with low-glucose suspend monitoring system (MiniMed 530G) for treatment of diabetes requiring exogenous insulin:** The U.S. Food and Drug Administration (FDA) approved the MiniMed 530G insulin delivery system (Medtronic plc, Dublin, Ireland) in September 2013. This intervention has been diffusing for more than 2 years and, therefore, no longer meets criteria for tracking; it was archived in the horizon scanning system in October 2015. The intervention has been in several prior AHRQ Potential High-Impact Interventions Reports, including June 2015. Commenters thought the system had potential to improve health outcomes by improving disease management and reducing hypoglycemic episodes, with likely widespread clinician and patient acceptance. In a May 2015 review published in *Diabetes Technology & Therapeutics* of almost 21,000 patients who used the MiniMed 530G system, Agrawal and colleagues reported that patients who continuously used the threshold-suspend feature showed a 62% reduction in sensor glucose values of 50 mg/dL or lower ($p<0.001$), and a 5.6% reduction in sensor glucose values of 300 mg/dL or higher, compared with data from nonusers ($p<0.001$). Further, when threshold-suspend was activated, the hypoglycemia reduction was more pronounced during nighttime than during daytime hours.

Eligible Topics Deemed High Impact

Diabetes Mellitus

Exenatide Continuous Subcutaneous Delivery (ITCA 650) for Treatment of Type 2 Diabetes

- **Key Facts:** ITCA 650 is extended-release exenatide (Bydureon™) delivered through a proprietary implantable system consisting of a “matchstick-sized osmotic pump” that is inserted subcutaneously to deliver a slow and consistent flow of exenatide. Exenatide, a GLP-1 receptor agonist that has been available since 2005, as an incretin mimetic that patients inject twice daily before meals. The ITCA 650 implant is intended to be used for long-term subcutaneous delivery at a controlled rate for treating T2DM. ITCA 650 reportedly remains stable at body temperature for delivery up to 12 months, based on data presented thus far. The outpatient implantation procedure is performed by a physician and takes about 10 minutes.

In September 2015, ITCA 650’s manufacturer announced study results from the phase III FREEDOM-1 and FREEDOM-1 High Baseline (HBL) trials in a press release. According to the company, the 460-patient FREEDOM-1 trial met all key endpoints. ITCA 650 produced mean reductions in HbA_{1c} of 1.4% at 39 weeks of treatment. Over 39 weeks, patients who received 60 mcg/day lost a mean of 4 kg, compared with 2 kg in the placebo group. Investigators observed no new safety concerns for the implant. The company also reported that 60 patients in FREEDOM-1 HBL had a 3.4% mean reduction in HbA_{1c}, with 22% of patients achieving HbA_{1c} reductions of 4% or greater at 39 weeks. (We believe the results for HbA_{1c} that the company stated as percent changes should instead be expressed as percentage points.) In August 2015, the company announced positive results from the 535-patient, phase III FREEDOM-2 trial in a press release. According to the company, ITCA

650 reduced HbA_{1c} levels by 1.5% compared with 0.8% for the DPP-4 inhibitor sitagliptin ($p<0.001$) after 52 weeks. The company also reported that patients who received ITCA 650 demonstrated significantly greater weight loss compared with patients who received sitagliptin (-4 kg vs. -1.3 kg; $p<0.001$). The manufacturer expects to file for regulatory approval of ITCA 650 to the U.S. Food and Drug Administration (FDA) in the first half of 2016. No information is available about anticipated costs.

- **Key Expert Comments:** Experts generally agreed on the need for effective T2DM treatments, citing patient adherence issues and the inconsistent efficacy of available treatments. They agreed on the potential of this intervention to reduce the burden of frequent injections and to provide consistent, effective treatment. Most experts opined that both clinicians and patients would be likely to accept this intervention. One expert anticipated wide physician adoption if the procedure is reimbursed separately to become a new revenue stream. Most experts predicted that the initial cost of the device would likely be offset by the long-term savings from reduced disease-related complications, if proven effective.
- **High-Impact Potential:** Lower end of the high-impact-potential range

Metabolic Surgery for Treatment of Type 2 Diabetes Mellitus Regardless of Patient BMI

- **Key Facts:** Metabolic surgery for T2DM has evolved as an intervention intended to induce remission in patients who have been unable to achieve adequate blood glucose control with first- and second-line therapy. Investigators have observed that bariatric surgery to reduce body weight in obese patients also offered an additional benefit of restoring metabolic imbalances and promoting diabetes remission in many patients. Metabolic surgeries for T2DM have been typically classified as purely restrictive, restrictive/malabsorptive, or purely malabsorptive. Restrictive procedures limit food consumption, while malabsorptive procedures reduce food absorption. Researchers hypothesize that the effect of metabolic surgeries extend beyond those of malabsorptive and restrictive strategies. Although the exact mechanisms of diabetes remission are unclear, researchers believe they are associated with multiple changes to patient anatomy and physiology, resulting in metabolic alterations.

In November 2015, Aminian and colleagues reported that in Cleveland Clinic study results released on Newswise, metabolic surgery was generally safe in patients with T2DM and body mass index (BMI) of 35 kg/m² or less. According to investigators, 30-day postoperative mortality was 0.2%, and the cumulative rate of postoperative adverse events was 4%.

Also in November 2015, Inge and colleagues reported that bariatric surgery in adolescents was generally safe and improved several health measures at 3-year followup. At 3 years after surgery, mean weight loss among the entire study population was 41 kg (90 lb), with a mean percentage weight loss of 27%. Within 3 years after surgery, 95% of patients with T2DM at baseline had remission of T2DM, and after 3 years, 76% of patients with prediabetes at baseline had remission of prediabetes. Further, remission of other conditions was also observed after 3 years, including 86% of patients with baseline abnormal kidney function, 66% of patients with baseline dyslipidemia, and 74% of patients with elevated baseline blood pressure. Patients reported an average 42.6% improvement in weight-related quality of life on the Impact of Weight on Quality of Life–Kids scale. However, after 3 years, investigators observed hypoferritinemia (abnormally low levels of the iron-storage protein ferritin) in 57% of patients.

Cost of metabolic surgery are similar to those for bariatric surgery and may vary depending on the surgical procedure used and whether it is minimally invasive or open surgery. Our searches of 11 representative, private, third-party payers that publish their coverage policies online found 9 outlining coverage for bariatric or metabolic surgery for obesity under certain conditions, but these policies do not address metabolic surgery for treating T2DM. Furthermore, we found no major payers with policies covering bariatric or metabolic surgery for patients with BMIs lower than 35 kg/m².

- **Key Expert Comments:** Most experts commenting saw a large unmet need for better management of individuals with T2DM. Several experts noted that metabolic surgery's potential to resolve T2DM rather than just manage the condition could potentially fill a large unmet need in improving patient health. According to most experts, metabolic surgery represents a substantial disruption to how most patients with T2DM are managed, compared with more conservative options such as pharmacotherapy and diet and lifestyle modification. Overall, experts expected that established bariatric surgery programs could add metabolic surgery to their programs with minimal disruption because insurance companies do not generally cover it. If insurance coverage becomes widely available and substantial patient demand develops, the programs would experience greater disruption trying to meet the need for surgical services.
- **High-Impact Potential:** High

Ultra-Rapid-Acting Inhaled Insulin (Technosphere Insulin Inhalation System With Afrezza) for Treating Diabetes That Requires Insulin

Key Facts: The Technosphere[®] insulin inhalation system with Afrezza[®] powdered insulin is a noninjectable, rapid-acting form of prandial (mealtime) insulin therapy intended to improve glycemic control in adult patients with T1DM or T2DM. The device size is small, and fits in the palm of the user's hand. In June 2014, FDA approved Afrezza for improving glycemic control in adults with diabetes mellitus. FDA required a Risk Evaluation and Mitigation Strategy (REMS) for Afrezza approval, informing prescribers about potential associated risks including the serious risk of acute bronchospasm. FDA recommends that Afrezza should not be used in patients with chronic lung disease, such as asthma or chronic obstructive pulmonary disease, because of this risk. Inhaled insulin has not been compared to injected insulin in large randomized, controlled trials. Available data reported by the manufacturers suggest that Afrezza therapy was associated with reduced pulmonary function that occurred during the first 3 months of therapy and persisted over 2 years.

In February 2015, the co-developers initiated a commercial rollout of prescription Afrezza to U.S. retail pharmacies. As of December 2015, Afrezza reportedly cost from about \$230 for a 90-cartridge kit at the 4-unit dose level to about \$310 for a kit containing 30 cartridges of 4 units each and 60 cartridges of 8 units each, at U.S. retail pharmacies. In December 2015, the drug manufacturer reported \$17.1 million in Afrezza sales for the first 9 months of 2015; however, the company also reported a total corporate loss of more than \$90 million for the same period, casting doubt on its long-term viability unless sales pick up dramatically in 2016.

- **Key Expert Comments:** Experts anticipated that the growing population with diabetes increases the importance of new developments to improve patient adherence to recommended therapy. Experts generally expected wide acceptance for inhaled insulin from prescribing physicians and patients. Some experts thought that higher costs than injectable insulin and availability of insurance coverage could affect access to this therapy for less-

affluent patients. Experts anticipated minimum disruption overall to health care infrastructure and patient management. However, several experts noted that patients will need to be screened for pulmonary conditions to be eligible for inhaled insulin.

- **High-Impact Potential:** Lower end of the high-impact-potential range

Diabetic Macular Degeneration

Fluocinolone Acetonide Implant (Iluvien) for Treatment of Diabetic Macular Edema

- **Key Facts:** Laser photocoagulation to halt vision loss is the standard treatment for DME, but this treatment cannot reverse vision loss that has already occurred and somewhat increases the risk of losing peripheral, night, or color vision. Injections of steroids or other agents may be used to treat DME but require repeated intravitreal injections to maintain therapeutic effect. Iluvien is a tiny tube containing the steroid fluocinolone acetonide that is injected once into the back of the eye and releases the drug slowly over 3 years to provide a combined vasoconstrictive and anti-inflammatory effect. In September 2014, FDA approved Iluvien for treating DME in patients “who have been previously treated with a course of corticosteroids and did not have a clinically significant rise in intraocular pressure.” Fluocinolone acetonide’s potential risk of increasing intraocular pressure might dissuade some physicians from embracing fluocinolone acetonide implants to treat DME until a larger body of evidence becomes available. In November 2015, the manufacturer reported that Iluvien treatment slowed progression of diabetic retinopathy compared with sham treatment in the phase III FAME™ study. Patients received a mean of 1.3 injected implants over the study duration. At 3-year followup, 17% of Iluvien-treated eyes showed progressive diabetic retinopathy that required additional intervention compared with 31% of sham-treated eyes ($p<0.001$). The manufacturer has reported “strong” (but nonspecific) Iluvien sales that may be bolstered by a new procedure-related billing code that will become effective in 2016.
- **Key Expert Comments:** Overall, experts commenting on this intervention opined that this intervention could offer a long-lasting, single-procedure pharmacotherapy as an alternative to laser photocoagulation or repeated injections of ranibizumab (Lucentis®) or other agents for treating DME. Experts expressed concerns regarding potential adverse events, including cataracts and increased intraocular pressure. Experts generally agreed that this intervention has the potential to be accepted by patients and clinicians because it may offer benefit up to 3 years. However, several experts commented that the risk of adverse events could affect patient and clinician adoption. Several experts noted that the intervention has the potential to reduce per-patient costs of treatment. However, experts also cautioned that cost savings could be nullified if patients need to be treated for device-related adverse events, such as cataracts or glaucoma.
- **High-Impact Potential:** Lower end of the high-impact-potential range

Diabetes Mellitus Interventions

Exenatide Continuous Subcutaneous Delivery (ITCA 650) for Treatment of Type 2 Diabetes

Unmet need: Despite the availability of oral antidiabetes drugs, many patients with type 2 diabetes mellitus (T2DM) do not meet treatment goals and require additional therapy with one of two types of injected antidiabetic agents: subcutaneous insulin or a glucagon-like peptide-1 (GLP-1) receptor agonist, also called an incretin mimetic.¹ Incretin mimetics have become standard treatments to improve glycemic control.² However, the GLP-1 receptor agonists approved by the U.S. Food and Drug Administration (FDA)—exenatide (Byetta[®]), liraglutide (Victoza[®]), and exenatide extended release (Bydureon[™])—require twice-daily, once-daily, or once-weekly dosing, respectively, by subcutaneous injection.^{3,4} More convenient dosing could potentially improve adherence to treatment recommendations and patient outcomes.

Intervention: ITCA 650 is a matchstick-sized, implantable device that is intended to deliver a steady dose of an incretin mimetic, exenatide, using a proprietary delivery system (Duros[®] technology) for up to 12 months.⁵ Exenatide, which has been available since 2005, is an incretin mimetic that patients inject twice daily, before meals. The new Duros delivery system is intended to deliver the drug subcutaneously, at a controlled rate over the long term. It has been used commercially since 2000 in a leuprolide acetate implant (Viadur[®]) for treating advanced prostate cancer.⁶

The system is a miniature osmotic pump that essentially functions as a syringe.⁶ Within a tubular titanium shell, the system contains a drug reservoir and an osmotic agent separated by a piston. Adjacent to the osmotic agent is a semipermeable membrane. The osmotic agent steadily draws water from the body across the membrane, which exerts pressure on the piston, forcing a steady flow of drug out of a small pore or diffusion moderator on the opposite side of the pump. Studies have demonstrated that the formulation of exenatide used in ITCA 650 is stable within the Duros pump for at least 1 year at body temperature, potentially allowing once-yearly system implantation.⁷

A physician inserts ITCA 650 under the skin during an outpatient procedure that takes 10-15 minutes.^{8,9} Clinicians can remove or replace the device in a similarly short procedure. In phase III clinical trials, the device is intended to deliver a dose of 40 or 60 mcg of exenatide per day.¹⁰⁻¹²

Clinical trials: The manufacturer is evaluating ITCA 650 in its FREEDOM clinical program, which is expected to include more than 4,000 patients at 500 clinical trial sites in more than 30 countries. The studies will include a broad range of patients whose diabetes is uncontrolled by oral antidiabetes medications including metformin and metformin-based combinations.^{10,13}

In September 2015 at the European Association for the Study of Diabetes meeting in Stockholm, Sweden, the company announced results from two phase III trials in the FREEDOM program (FREEDOM-1 and FREEDOM-1 High Baseline [HBL]) in a press release.¹¹ FREEDOM-1, a double-blind, placebo-controlled study, demonstrated positive results for ITCA 650 when added to diet and exercise with or without standard oral diabetes medications, for those patients who were not at goal. At baseline, 460 patients had a mean glycated hemoglobin (HbA_{1c}) level of 8.5%, mean body mass index (BMI) of 33.5 kg/m², and had had diabetes for a mean of 9 years since diagnosis. Almost 90% of patients were being treated with up to 3 oral antidiabetic medications. Patients were randomly assigned to receive placebo or ITCA 650 delivering either 40 or 60 mcg/day. According to the manufacturer, all primary and secondary endpoints were met. ITCA 650 produced sustained mean reductions in HbA_{1c} of 1.4% at 39 weeks of treatment (in a modified intent-to-treat [mITT] population). Patients on a background regimen including a sulfonylurea drug (47% of patients) had a mean HbA_{1c} reduction of 1.2%. Patients on a non-sulfonylurea background regimen, including

primarily metformin-based regimens (about 40% of patients), or diet-and-exercise regimens (about 11% of patients), showed a mean HbA_{1c} reduction of 1.7%. “Patients...lost a mean of 4 kg in the 60 mcg/d ITCA 650 dose group vs. 2 kg in the placebo group at Week 39, a difference that was statistically significant,” the company reported. Investigators observed no new safety concerns beyond what is known for the GLP-1 receptor agonist class.¹¹ In previous research, the most commonly reported adverse events associated with GLP-1 receptor agonist therapy include nausea and/or vomiting that typically diminishes over time; diarrhea; and less commonly, hypoglycemia, especially when combined with an insulin secretagogue, such as a sulfonylurea.^{14,15} The company reported that tolerability was similar between the 40 mcg per day and the higher 60 mcg per day dose groups. According to the press release, “There was a low single-digit discontinuation rate for nausea... Other adverse events associated with the administration site and the procedures to place and remove the ITCA 650 were generally mild and transient. Discontinuations due to procedures and administration site adverse events were also a very low single digit rate across each arm of the 39-week study.”¹¹

The press release also reported on 60 patients in FREEDOM-1 HBL who had a 10.8% mean HbA_{1c} level (range, >10% but ≤12%), a mean 32.0 kg/m² BMI, and mean 9-year diabetes duration at baseline. By 39 weeks, patients had a 3.4% mean reduction in HbA_{1c}, with 22% of patients achieving HbA_{1c} reductions of 4% or greater and 25% of patients achieving an HbA_{1c} level of less than 7% at the last observation carried forward endpoint. Investigators observed weight loss in patients that did not achieve statistical significance. “The most common adverse events were consistent with the known effects of exenatide and the GLP-1 receptor agonist class (mainly gastrointestinal). Most were observed early in the course of treatment and improved over time,” the company stated.¹¹

In August 2015, the company announced positive results from the phase III FREEDOM-2 trial in a press release.¹² FREEDOM-2 compared ITCA 650 to the dipeptidyl peptidase-4 (DPP-4) inhibitor sitagliptin (Januvia®) in 535 adults with HbA_{1c} levels between 7.5% and 10.5% on background metformin therapy. Patients were randomly assigned to receive ITCA 650 delivering 60 mcg/day plus once-daily oral placebo or oral sitagliptin 100 mg once daily plus ITCA 650 placebo. “Patients treated with ITCA 650 60 mcg experienced superior reductions in HbA_{1c} versus those treated with Januvia (sitagliptin) 100 mg (-1.5% versus -0.8%; p<0.001)” after 52 weeks—the primary endpoint, the company reported. Further, the company stated that patients who received ITCA 650 demonstrated significantly greater weight loss than did patients who received sitagliptin 100 mg (-4 kg vs. -1.3 kg; p<0.001). The company announced that at 52 weeks, “ITCA 650 results were superior vs. Januvia 100 mg” for the trial’s 3 secondary endpoints: a composite of glucose reductions of more than 0.5% and weight loss of 2 kg or greater, a change in body weight, and proportion of patients achieving the HbA_{1c} target recommended by the American Diabetes Association (ADA) of below 7.0%. ITCA 650 showed an overall and gastrointestinal tolerability profile similar to that seen in FREEDOM-1. “Discontinuations for nausea were in the low single digits over the full 12 months of treatment. There were no cases of major hypoglycemia in either study arm, and minor events of hypoglycemia were reported in the low single digits for both study arms. The placements and removals of ITCA 650 were very well tolerated, and the rate of minor infections at the application site was less than 1% of all procedures in the trial,” the company stated.¹²

Manufacturer and regulatory status: Intarcia Therapeutics, Inc. (Hayward, CA), is developing the ITCA 650 system for continuous subcutaneous delivery of extended-release exenatide for injection (Bydureon™), made by AstraZeneca (London, UK). In November 2014, Intarcia announced a partnership that grants exclusive rights to Servier (Suresnes, France) to market

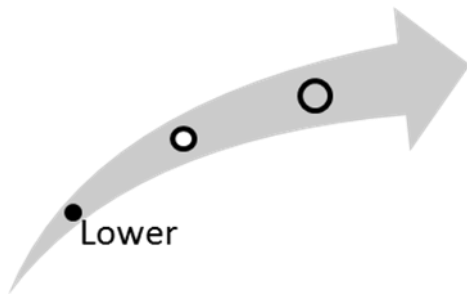
the ITCA 650 system outside of the United States and Japan.¹⁶ The company anticipates submitting a premarket approval application to FDA in the first half of 2016.^{5,12}

Diffusion: If it receives FDA approval, ITCA 650 is most likely to compete with injected exenatide extended release (administered once weekly) and liraglutide (administered once daily).^{3,4,17} The cost for ITCA 650 has not been determined, but it will likely be priced at a slight premium to existing injectable exenatide formulations because of its novelty and convenience.¹⁸ Although ITCA 650 use would add to the upfront cost of therapy, it could potentially save money if it improves patient adherence to prescribed treatment, slows disease progression and development of secondary complications, and eliminates the attendant health services needed to treat those complications.

Clinical Pathway at Point of This Intervention

T2DM typically occurs in middle age or later, although incidence in a younger population has been growing as a result of the obesity epidemic. Initial treatment includes dietary modification, exercise, and self-monitoring of blood glucose. First-line drug therapies include biguanides, sulfonylureas, alpha-glucosidase inhibitors, insulin sensitizers, insulin secretagogues, and DPP-4 inhibitors. Some patients require combination drug therapy of agents with different mechanisms of action for additive therapeutic effects and better glycemic control. Despite the availability of oral antidiabetes drugs, many patients do not achieve treatment goals and require additional therapy with an injected antidiabetes agent: subcutaneous insulin or a GLP-1 receptor agonist.¹ The ITCA 650 implant would be used in place of injectable GLP-1 receptor agonists.

Figure 1. Overall high-impact potential: exenatide continuous subcutaneous delivery (ITCA 650) for treatment of type 2 diabetes



Overall, experts commenting on this intervention agreed on the need for more effective T2DM treatments, citing patient adherence issues and the lack of efficacy of available treatments. Experts commented that this intervention has the potential to improve patient health by reducing the burden of frequent injections. Experts agreed on the potential for widespread acceptance by both clinicians and patients. Physicians would be attracted by the potential to reduce treatment variability through consistent drug delivery. Patients would likely accept this intervention because it may replace frequent injections with an annual procedure. Some experts thought that the initial cost of the device could be offset by long-term savings from reduced disease-related complications. Based on this input, our overall assessment is that this intervention is in the lower end of the high-impact-potential range.

Results and Discussion

Six experts, with clinical, research, and health systems backgrounds, provided perspectives on ITCA 650 (subcutaneous exenatide).¹⁹⁻²⁴ We have organized the following discussion of expert comments by the parameters on which they commented.

Unmet need and health outcomes: Most experts agreed that a large unmet need exists for new interventions that may help patients with T2DM better meet their treatment goals, given the large and growing population with diabetes. One health systems expert stated, “Adherence issues with oral drugs and insulin are significant.”²⁴ However, another health systems expert thought that the availability of several other medications for T2DM lessened the unmet need that ITCA 650 purports to fulfill.¹⁹ Most experts thought that ITCA 650 has good potential to improve patient health and to fulfill the unmet need compared with available treatments. One clinical expert noted, “Lack of compliance to current type 2 diabetes drugs is a major contributor to poor glycemic control and microvascular complications of type 2 diabetes. ITCA 650 is likely to improve glycemic control because of its long duration of action. The preliminary data indicate a dose-dependent improvement in glycemic control in patients treated with ITCA 650.”²¹ However, two experts, with health systems and research backgrounds, were less confident that the intervention would improve patient health or fulfill an unmet need, and they wanted to see additional outcomes data from larger trials before fully embracing ITCA 650.^{19,22} One research expert noted, “For some patients, particularly those who have struggled with complying to treatment with self-injectable exenatide treatments, ITCA 650 might improve health outcomes. However, in general, this treatment does nothing to change a patient’s lifestyle approach.”²²

Acceptance and adoption: Overall, experts anticipated wide acceptance from physicians for improving the standardization of drug delivery. One clinical expert stated, “The current management of type 2 diabetes is largely ineffective. ITCA 650 is likely to gain wide acceptance among clinicians because the device is easy to implant, and the treatment is likely to improve glycemic control and reduce diabetes-related complications.”²¹ One research expert stated, “As a more controlled treatment option for patients with T2DM, I foresee clinicians accepting ITCA 650. Offering this new form of exenatide therapy might also attract more patients and potentially even offer clinicians a new revenue stream, if the implantation procedure is charged separately.”²² Experts thought that a large proportion of patients would choose this device for convenience and the possibility of improved outcomes through more consistent drug delivery, although some patients may continue to prefer regular injections to an implanted device. One clinical expert stated, “Most of the current drugs for type 2 diabetes have to be administered frequently, which leads to poor compliance. Most patients are likely to use ITCA because it offers a long-term possibility of improving glycemic control and preventing diabetes-related complications.”²¹ Experts were somewhat divergent in estimating ITCA 650’s cost impact. Most experts thought that the intervention would likely cost somewhat more than injectable exenatide or comparable drugs but holds some potential to reduce costs by lowering incidence of complications through more consistent drug delivery. In a contrasting view, one health systems expert opined, “I don’t agree with potential to lower longer term costs. The out-of-sight, out of mind concept may play here, with patients not adhering to dietary/exercise regimens since they don’t have to take/check insulin twice a day.”¹⁹

Health care delivery infrastructure and patient management: Experts generally anticipated that introducing ITCA 650 would create little disruption to either health care infrastructure or management of patients with T2DM. Clinicians would likely require minimal training in office-based device implantation, the experts thought. Likewise, the experts expected that patient followup would likely be similar because this patient population typically is monitored closely. One health

systems expert suspected that the more consistent drug delivery might result in fewer diabetes-related emergencies necessitating acute treatment.¹⁹ But this expert also stated, “I fear that physicians will prescribe and walk away from the patient until the next insertion date, without providing the lifestyle management and encouragement necessary for type 2 diabetes mellitus.”¹⁹

Health disparities: Generally, the experts thought that ITCA would likely have a modest impact on health care disparities. However, they thought a disparity could emerge if the implantable drug dispenser is not covered by health insurers. If reimbursement were not widely available, patients with lower socioeconomic status might be less likely to have access to ITCA 650, and these patients are often more widely affected by diabetes, most experts noted. One research expert noted, “As long as the medication were covered by payers, there should not be a large impact on health disparities. This device may be very important in reducing disparities in patient sub-populations who may not be able to self-inject exenatide, and for whom other oral medications are either not appropriate or insufficient to manage their blood glucose.”²⁰

Metabolic Surgery for Treatment of Type 2 Diabetes Mellitus Regardless of Patient BMI

Unmet need: Despite availability of new diabetes medications, behavioral and lifestyle therapies, glucose monitors, insulin pumps, and treatment protocols, two-thirds of patients with T2DM, especially those requiring insulin therapy, do not achieve adequate glycemic control. This increases their risk of secondary complications, including cardiovascular disease, nephropathy, neuropathy, and retinopathy.²⁵⁻²⁷ Observations that T2DM has resolved completely after various bariatric surgery modalities—independent of any resulting weight loss—in many morbidly obese patients who also had diabetes led to a study of the surgery’s impact on less obese patients with T2DM, and similar observations were made. This led to the reframing of bariatric surgery as metabolic surgery for treating refractory T2DM in patients who have been unable to achieve adequate glucose control with first- and second-line therapy, regardless of the patient’s BMI. The approach focuses less on weight loss *per se* and more on addressing the metabolic abnormalities involved in diabetes.^{28,29}

Intervention: Metabolic surgery for T2DM has evolved as a surgical intervention intended to induce remission in patients who have been unable to achieve adequate blood glucose control with first- and second-line therapy. Although initially termed bariatric surgery and used to treat morbid obesity (BMI more than 35 kg/m² with at least one comorbidity [e.g., diabetes, hypertension] or with BMI of more than 40 kg/m²), this approach has been explored as a diabetes treatment regardless of patient BMI and independent of weight-loss goals.²⁹ Some clinical researchers believe that BMI-based criteria for bariatric surgery are not appropriate for determining eligibility in patients with T2DM because the primary goal of bariatric surgery (weight loss) is different from the primary goal of metabolic surgery (restoring metabolic dysfunction responsible for T2DM). Therefore, many obesity- or bariatric-surgery professional societies have added the term “metabolic” to their organization names, and many centers that use the surgery for weight reduction and separately for T2DM management include “metabolic” when referring to their surgery centers.^{30,31}

This distinction has contributed to a paradigm shift in surgery for T2DM from surgery directed at obesity alone to surgery directed at restoring metabolic imbalances, thereby loosening patient eligibility criteria from a focus purely on high BMI to a focus on treatment-refractory T2DM.³² A consensus has been building that the metabolic improvements (e.g., normalized glycemia) observed after metabolic surgery often precede weight loss in obese patients, and the improvements have occurred even in patients with BMIs lower than 35 kg/m² and lower even than 30 kg/m².³² This suggests that a metabolic change, not weight loss, is likely responsible for the reduction or reversal of diabetes in these patients.³²⁻³⁴

Metabolic surgeries for T2DM have been typically classified as purely restrictive, restrictive/malabsorptive, or purely malabsorptive; restrictive procedures limit food consumption, while malabsorptive procedures reduce food absorption.³⁵ However, as the effects of various procedures become more evident, this terminology has become less useful for addressing the issues of metabolic surgery.²⁹ Researchers hypothesize that the effects of metabolic surgery extend beyond those of malabsorptive and restrictive strategies. Although the exact mechanisms of diabetes remission are unclear, researchers believe they are associated with multiple changes to patient anatomy and physiology, resulting in metabolic alterations.³⁶⁻³⁸

Most metabolic surgery procedures are done laparoscopically; however, laparoscopic surgery may be difficult in patients with intra-abdominal adhesions or hernias. Therefore, metabolic surgery

may sometimes still be performed as an open procedure.^{29,35} Procedures most often considered to be metabolic surgeries are discussed here.

Purely restrictive metabolic surgical procedures. Laparoscopic adjustable gastric banding (LAGB) and vertical sleeve gastrectomy (VSG) reduce the stomach size to limit the rate and volume of food intake, decrease appetite, and increase feelings of satiety. In LAGB, a surgeon reversibly reduces stomach size by placing a band around the upper part of the stomach. In some studies, LAGB has been associated with T2DM resolution (or improvement) in as many as 80% of patients and excess weight loss of more than 30% (as much as 70%).^{39,40} VSG is an irreversible surgical procedure in which the surgeon excises a large portion of the stomach.^{41,42}

Restrictive/malabsorptive procedures. Roux-en-Y gastric bypass (RYGB) and biliopancreatic diversion are performed with or without duodenal switch. RYGB is primarily restrictive, although it has both restrictive and malabsorptive features. The surgeon partitions the stomach to form a small, 30 mL pouch where food will enter.³⁹ The surgeon then connects the distal small intestine to this gastric pouch. This connection creates the “Roux,” or alimentary limb of the Y-shaped construction. Next, the surgeon connects the duodenum portion of the upper small intestine to a distal section of the small intestine, thereby bypassing the duodenum and upper jejunum, creating the second limb of the “Y.”³⁹ In biliopancreatic diversion, a surgeon performs a 60% distal gastric resection and creates a stapled closure of the duodenal stump to result in a stomach volume of about 300 mL.³⁹ With the duodenal switch, the surgeon performs a proximal gastric resection leaving the pylorus to control food drainage. Food and digestive nutrients mix in the remaining 50 cm of the bowel.^{39,43}

Purely malabsorptive procedures. These procedures are the jejunoileal bypass (JB) and the duodenojejunal bypass (DB).^{32,36} In JB, a surgeon creates an ileal interposition linked to a diverted sleeve gastrectomy, thereby connecting the ileum, the lowest part of the small intestine, to the proximal intestine. This keeps digestive nutrients away from the bowel and limits small intestine length and absorptive surface area.³⁹ DB is a stomach-sparing bypass in which surgeons partially transect the duodenum 2 cm distal to the pylorus and perform duodenojejunal anastomosis to manipulate the intestine.^{43,44} A device known as an endoluminal sleeve intended to block nutrient absorption from the stomach to the jejunum is commercially available outside the United States, but the manufacturer ended further development in the United States in late 2015 after several cases of hepatic abscess halted U.S. trials.^{45,46}

Clinical trials: In November 2015, Aminian and colleagues reported that metabolic surgery in patients with lower BMI was generally safe, in an analysis of 1,003 patients with T2DM and BMI of 35 kg/m² or less (average BMI, 33.5 kg/m²) who underwent metabolic surgery between 2005 and 2013, including 46 patients with BMI of 30 or less. Patient data were collected from the American College of Surgeons National Surgical Quality Improvement Program database. Before surgery, 60% of patients were taking at least one oral medication for T2DM, and 40% of patients were taking insulin injections.⁴⁷ According to investigators, 30-day postoperative mortality was 0.2%, and the cumulative rate of postoperative adverse events was 4%. The average surgical time was 2 hours, and the average length of hospital stay was 2 days. Surgical procedures included gastric bypass (57%), gastric banding (23%), sleeve gastrectomy (19%), and duodenal switch (1%).⁴⁷

Also in November 2015, Inge and colleagues reported that bariatric surgery in adolescents was generally safe and improved several health measures at 3-year followup.⁴⁸ The study prospectively enrolled 242 patients with mean baseline age of 17±1.6 years and mean BMI of 53 kg/m² who were mostly female (75%) and white (72%). Enrolled patients underwent RYGB (n=161), sleeve gastrectomy (n=67), or adjustable gastric banding (n=14) at 5 U.S. centers between March 2007 and February 2012. At 3 years after surgery, mean weight loss among the entire study population was 41 kg (90 lb), with a mean percentage weight loss of 27% (95% confidence interval [CI], 25% to 29%). Mean percentage weight loss was 28% (95% CI, 25% to 30%) in the RYGB group and 26%

(95% CI, 22% to 30%) in the sleeve gastrectomy group. In 11 gastric banding patients for whom complete data were available, mean weight loss was 10.4 kg (23 lb) (95% CI, -26.5 to 5.7), and mean percent weight loss was 8.3% (95% CI, -19.8% to 3.2%); 36% (4 of 11) gastric banding patients had exceeded their baseline weight at 3 years. Additionally, one patient underwent band explantation and conversion to gastric bypass for band intolerance, two patients underwent operations for band or port complications, and one patient underwent band removal without conversion to another procedure. Within 3 years after surgery, 95% of the 29 patients with T2DM at baseline had remission of T2DM (95% CI, 85% to 100%), and 76% of 19 patients with prediabetes at baseline had remission of prediabetes after 3 years (95% CI, 56% to 97%). Further, 86% (95% CI, 72% to 100%) of 36 patients with baseline abnormal kidney function had remission of abnormal kidney function. Among 171 patients with dyslipidemia at baseline, 66% (95% CI, 57% to 74%) had remission of dyslipidemia after 3 years. Among 96 patients with elevated blood pressure at baseline, 74% (95% CI, 64% to 84%) had remission of elevated blood pressure after 3 years. Patient-reported weight-related quality of life improved from baseline on the Impact of Weight on Quality of Life–Kids scale (higher scores indicate higher quality of life), from 63 (95% CI, 61 to 65) to 83 (95% CI, 81 to 86), a 42.6% change (95% CI, 32.6% to 52.5%). However, after 3 years, investigators observed hypoferritinemia in 57% (95% CI, 50% to 65%) of patients (hypoferritinemia is an abnormally low level of ferritin, a protein that stores and releases iron into the blood); comparatively at baseline, 5% (95% CI, 2% to 8%) of patients had low ferritin levels. Overall, 13% (95% CI, 9% to 18%) of patients required one or more additional intra-abdominal procedures after the index bariatric surgery.⁴⁸

In November 2014, Muller-Stich and colleagues analyzed T2DM remission rates for 706 patients with T2DM and BMIs of less than 35 kg/m² enrolled in 5 randomized controlled trials and 6 observational clinical studies.⁴⁹ At followup from 12 to 36 months, metabolic surgery was associated with a higher T2DM remission rate (odds ratio [OR], 14.1; 95% CI, 6.7 to 29.9; $p < 0.001$), a higher rate of glycemic control (OR, 8.0; 95% CI, 4.2 to 15.2; $p < 0.001$) and a lower HbA_{1c} level (mean difference [MD]: -1.4%; 95% CI, -1.9% to -0.9%; $p < 0.001$) than medical treatment.⁴⁹ After metabolic surgery, lower values were seen for the following:⁴⁹

- BMI (MD, -5.5 kg/m²; 95% CI, -6.7 to -4.3 kg/m²; $p < 0.001$)
- Rate of arterial hypertension (OR, 0.25; 95% CI, 0.12 to 0.50; $p < 0.001$)
- Dyslipidemia (OR, 0.21; 95% CI, 0.10 to 0.44; $p < 0.001$)

In October 2014, Parikh and colleagues reported on remission rates and homeostatic model of insulin resistance (HOMA-IR) for 57 adults with T2DM and BMIs of 30–35 kg/m².⁵⁰ Investigators found that at 6 months, the surgery group had improved HOMA-IR, compared with the medical weight management group (-4.6 vs. +1.6; $p = 0.0004$) and higher diabetes remission (65% vs. 0%; $p < 0.0001$). The surgery group had lower HbA_{1c} levels than the medical management group (6.2 vs. 7.8; $p = 0.002$), lower fasting glucose (99.5 vs. 157 mg/dL; $p = 0.0068$), and fewer had T2DM medication requirements (20% vs. 88% of patients; $p < 0.0001$) at 6 months. The surgery group also lost more weight than the medical management group (7 vs. 1 kg/m² BMI decrease; $p < 0.0001$). Higher baseline sRAGE (soluble form of receptor for advanced glycation end products) was associated with better weight loss outcomes ($r = -0.641$; $p = 0.046$). No deaths occurred. Surgery was very effective short-term in patients with T2DM and BMIs of 30–35 kg/m². Investigators concluded that baseline sRAGE may predict which patients might be most likely to benefit from metabolic surgery.⁵⁰

Manufacturer and regulatory status: Surgical procedures are not subject to FDA approval; however, the bands used in one of the procedures, gastric banding (e.g., Lap-Band, Realize), are subject to FDA regulation. Searches identified four manufacturers that distribute and market devices

used for gastric band procedures.⁵¹⁻⁵⁴ Commercially available technologies for metabolic surgery include the following:

- Heliogast HAGA, HAGE Gastric Band by Helioscopie (Vienne, France)⁵³
- Lap-Band Adjustable Gastric Band by Allergan, Inc. (Irvine, CA)⁵¹
- Midband Adjustable Gastric Band by Médical Innovation Développement Co. (Dardilly, France)⁵⁴
- Realize adjustable gastric band by the Ethicon Endo-Surgery unit of Johnson & Johnson (New Brunswick, NJ)⁵²

Only one of the two FDA-approved approved devices has an indication that includes patients with BMIs of less than 35 kg/m², the Lap-Band.⁵⁵ The device is indicated for use in weight reduction for patients with BMIs of 40 kg/m² or more or 30–40 kg/m² with one or more obesity-related comorbid conditions.⁵⁵

Diffusion: Few reliable estimates of the diffusion of metabolic surgery are available because of the relative novelty of the procedure and varied technical approaches to performing it. A search of the U.S. National Clinical Trials Database (ClinicalTrials.gov) found 53 active trials (as of December 2015) evaluating some type of bariatric or metabolic surgery that mentioned effect on diabetes or diabetes-related measurements as one of the outcomes. At least for the near future, modest diffusion of metabolic surgery would be expected without adequate insurance coverage for the procedure.

Since February 2009, the U.S. Centers for Medicare and Medicaid Services (CMS) has had a national coverage determination titled “Surgery for Diabetes” that states, “Medicare currently covers bariatric surgery for persons with type 2 diabetes mellitus (T2DM) and a body mass index (BMI) ≥ 35 ” for whom medical treatment for obesity has not been successful.⁵⁶ Bariatric surgery remains noncovered for Medicare beneficiaries who have T2DM and a BMI of less than 35 kg/m². Eligible surgical procedures include open and laparoscopic RYGB, open and laparoscopic biliopancreatic diversion with duodenal switch, and LAGB.⁵⁶

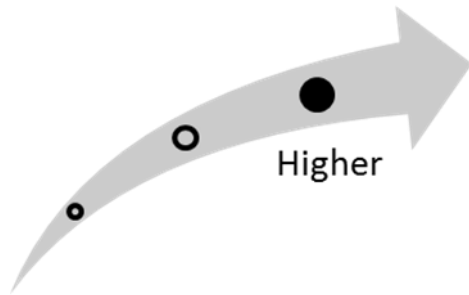
Our searches of 11 representative, private, third-party payers that publish their coverage policies online (i.e., Aetna, Anthem, Blue Cross/Blue Shield of Alabama, Blue Cross/Blue Shield of Massachusetts, CIGNA, HealthPartners, Humana, Medica, Regence, United Healthcare, Wellmark) found 9 outlining coverage for bariatric surgery for obesity, but these policies do not address metabolic surgery for treating T2DM. Furthermore, searches found no major payers with policies covering bariatric surgery for patients with BMIs lower than 35 kg/m². The policies on obesity surgery indicate that many of the benefit plans exclude coverage, but for the benefit plans that provide coverage, patients must have a BMI of more than 40 kg/m² or more than 35 kg/m² with a comorbidity.⁵⁷⁻⁶⁵ Two payers (Humana, Wellmark) indicate that patients who wish to undergo bariatric surgery may qualify for coverage if they receive a referral from their primary care physician. However, criteria for coverage are not provided by these payers.^{66,67}

Clinical Pathway at Point of This Intervention

Despite availability of new diabetes medications, behavioral and lifestyle therapies, glucose monitors, insulin pumps, and treatment protocols, two-thirds of patients with T2DM do not achieve adequate glycemic control. This increases their risk of secondary complications, including cardiovascular disease, nephropathy, neuropathy, and retinopathy.²⁵⁻²⁷ Clinical guidelines from the American Association of Clinical Endocrinologists, the Obesity Society, and the American Society for Metabolic & Bariatric Surgery state, “Patients with BMI of 30–34.9 kg/m² with diabetes or metabolic syndrome may also be offered a bariatric procedure although current evidence is limited by the number of subjects studied and lack of long-term data demonstrating net benefit.”²⁹ Thus,

bariatric surgery intended to produce benefit beyond weight loss, otherwise defined as metabolic surgery, could conceivably be offered to treat T2DM and reduce cardiometabolic risk factors in patients whose disease is inadequately managed with more conservative medical management and lifestyle modification.

Figure 2. Overall high-impact potential: metabolic surgery for treatment of type 2 diabetes mellitus regardless of patient BMI



Most experts cited a large unmet need for improving diabetes management, with an increasing population with T2DM adding to the potential unmet need. Several experts noted metabolic surgery’s potential to put T2DM into remission rather than just manage the condition as supporting its large potential to improve patient health and fill a large unmet need. Most experts thought that metabolic surgery would represent a substantial disruption to how patients with T2DM are managed, compared to medical management and diet and lifestyle modification. Overall, experts expected that established bariatric surgery programs could add metabolic surgery to their programs with minimal disruption, unless insurance coverage becomes widely available, in which case substantial patient demand could develop. Based on this input, our overall assessment is that this intervention is in the higher end of the high-impact-potential range.

Results and Discussion

Six experts, with clinical, research, and health systems backgrounds, provided perspectives on this intervention.⁶⁸⁻⁷³ One clinical expert reported consulting relationships with manufacturers of obesity-related medical devices.⁶⁹ This potential conflict of interest is balanced by other expert commenters who reported no potential conflicts of interest. We have organized the following discussion of expert comments by the parameters on which they commented.

Unmet need and health outcomes: Most experts cited a large unmet need for new therapeutic approaches to treat T2DM, given the growth of the T2DM population and the health risks and costs associated with complications from poorly managed disease. One research expert stated, “With close to 10% of the population affected by the disease and two-thirds of them not achieving adequate glycemic control, there exists an important gap to address.”⁷² One clinical expert noted, “There are millions of patients who may fit into the category of type 2 diabetes with BMI under 35. Metabolic surgery would provide an opportunity for improvement in many cardiovascular risk factors along with weight loss with fewer medications.”⁷⁰ However, one research expert saw little unmet need for metabolic surgery to fill, stating, “Despite the overwhelming number of patients with T2DM, there is really little to no need for an invasive intervention when a variety of other treatment options exist AND the disease is completely resolvable through diet and lifestyle changes.”⁷¹ Most experts cited metabolic surgery’s overall potential to improve health outcomes and fill the unmet need.^{68-70,72,73} One research expert noted “pretty clear evidence that surgery improves diabetes, or even resolves it.”⁷³ One clinical expert stated, “There is a large potential to improve health outcomes with metabolic surgery. Unfortunately, at present we only have surrogate

outcomes. Standard bariatric surgery has suggested fewer cardiovascular events and possibly fewer cancers in observational studies. Long term outcomes are needed with metabolic surgery vs. best medical therapy.”⁷⁰ Another clinical expert stated, “Metabolic surgery has the potential to put diabetes into remission. Pharmacotherapy can only manage the condition.”⁶⁹ One research expert cautioned, “While the data suggest that metabolic surgery may help control T2DM, the long term side effects of such intervention need to be considered as well as patient compliance with any required lifestyle changes.”⁷² Another research expert generally disagreed, stating, “I still firmly believe that there are much better/favorable options for addressing T2DM, such as diet and lifestyle changes. One would think that a patient who is willing to modify his/her lifestyle after metabolic surgery (to cope with post-procedural effect), would be more than willing to pull their ‘all’ into this approach in an effort to avoid needing surgery in the first place.”⁷¹

Acceptance and adoption: Experts were divided on acceptance by physicians and patients. Generally, most experts believed that acceptance by both groups could increase in the future if clinical data show long-term safety and efficacy and if third-party payer coverage becomes available. Most experts did not anticipate metabolic surgery would be the first choice for most physicians or their patients. One clinical expert stated, “There is great potential here. However, patients, providers, and payors would need to be educated more effectively about that potential.... At present, many individuals with BMIs between 35 and 45 do not believe they are candidates for bariatric surgery. Many believe the procedures are reserved for those who weigh 600 lbs. Thus, lowering the BMI cutoff would not have a dramatic impact on patient volume for some time.”⁶⁹ This clinical expert added, “Endocrinologists will fight this to the death, as it would threaten their livelihood. Individuals who are anti-bariatric surgery currently would be opposed as well.”⁶⁹ Another clinical expert stated, “I think initially most clinicians would be hesitant to refer patients who are relatively healthy with BMI under 35 to surgery. If outcomes are shown to be better than a best medical approach and surgery is safe (as it is at present for bariatric surgery), acceptance should increase.”⁷⁰ This clinical expert expected a similar situation with patients: “While some patients would welcome this surgery as an alternative to a medical approach, I believe that many would avoid it initially. Over time, acceptance would increase, especially if the surgery and program is covered by insurance and could be done as an outpatient or with minimal hospital stay.”⁷⁰ One research expert stated, “I expect that for eligible patients, clinicians would be willing to prescribe this procedure. It could increase the number of patients receiving this type of surgery, which could increase revenues for the performing clinician. In addition, since it has been shown to be effective, it would provide clinicians the power to resolve their patients’ disease rather than asking them to make the changes necessary to do so themselves.”⁷¹

Health care delivery infrastructure and patient management: Overall, experts expected metabolic surgery to have a modest impact on established bariatric surgery programs in the short term because the experienced staff and surgical facilities are already in place. However, most experts thought metabolic surgery could represent a substantially greater disruption to health care infrastructure if the procedure were widely reimbursed by insurance plans and if patient demand increased, given the large population with T2DM. One research expert stated, “If all patients with diabetes had surgery, this would have a HUGE impact on the healthcare system, due to the multidisciplinary nature of surgery.”⁷³ Another research expert stated, “Performing surgery for metabolic disease would be a departure from how healthcare is currently delivered to these patients. Nevertheless, these types of surgeries are already being performed in patients who are obese or overweight with comorbidities. Therefore, for facilities already offering bariatric surgery, adoption of metabolic surgery is not likely to cause a large disruption. These centers would, however, have to accommodate a potential increase in patient volume and educate staff on T2DM.”⁷¹ A clinical expert stated, “If metabolic surgery for BMI under 35 were available and approved by insurance,

there could be a significant influx of patients seeking this surgery. The clinics that prepare patients for bariatric surgery might need to hire extra staff including surgeons, behavioral providers, dietitians, and other medical providers.”⁷⁰ Another clinical expert stated, “If the recommended BMI criteria were to decrease, and payors would agree to cover those procedures, then volumes would increase and more professionals would have to enter the field. However, these scenarios would take years to play out.”⁶⁹ Several experts noted that metabolic surgery would be a substantial change from how most patients with T2DM are managed.^{68,71-73} One research expert stated, “Patients with T2DM have not conventionally been treated via inpatient, invasive, and in some cases irreversible, procedures such as...metabolic surgery. Therefore, an increase in the number of patients with T2DM seeking metabolic surgery would likely cause a substantial change in how patients with the disease are currently managed.”⁷¹ A health systems expert noted, “As there is a long-term follow-up care needed for these types of surgery, there will be a disruption to how the care is carried out. These patients have to be on vitamins supplements, etc., for the rest of their lives as not as much nutrients are absorbed.”⁶⁸ However, two clinical experts anticipated small change to how most patients are managed because they expected that few patients would opt for metabolic surgery if given a choice, at least for the near future.^{69,70}

Health disparities: Experts offered mixed opinion on whether metabolic surgery could affect disparities. On one hand, several experts thought metabolic surgery could offer a substantial improvement in diabetes control and possible remission in less-affluent patients who are more widely affected by diabetes.^{69-71,73} One clinical expert stated, “The use of bariatric/metabolic surgery to treat obesity/T2DM is a huge health disparities issue. While minority groups are most commonly affected, they are far less likely to receive surgical treatment. In addition, those individuals from lower socioeconomic groups face environmental and economic challenges that make lifestyle modification and pharmacotherapy treatments less effective. Surgical intervention may represent their best chance to effectively treat obesity and T2DM.”⁶⁹ On the other hand, limited coverage from health plans has potential to increase disparities by restricting access to metabolic surgery for many patients who would likely benefit from it.^{68,70-73} One research expert stated, “Diabetes is overrepresented in poorer people. If they have less access to treatment, then disparities will increase.”⁷³ A clinical expert noted, “The potential to affect health disparities would depend on insurance coverage for metabolic surgery if it becomes a standard of care. If not covered by most insurances, those who could afford to pay for the surgery out of pocket would have an advantage leading to a difference in access.”⁷⁰

Ultra-Rapid-Acting Inhaled Insulin (Technosphere Insulin Inhalation System With Afrezza) for Treating Diabetes That Requires Insulin

Unmet need: Despite available insulin formulations, pumps, and oral antidiabetic medications, optimal glycemic control remains a challenge for many patients with diabetes who require insulin therapy.⁷⁴ Patients who do not achieve adequate glycemic control have an increased risk of secondary complications (i.e., cardiovascular disease, retinopathy, nephropathy, neuropathy).^{75,76} Difficulties with adherence to available insulin delivery methods and self-monitoring are two of the factors affecting adequate management.^{74,77} Therefore, a need exists for improved insulin delivery methods to aid adherence and improve glycemic control.

Intervention: The Technosphere[®] insulin inhalation system with Afrezza[®] powdered insulin is a noninjectable form of insulin therapy intended to improve glycemic control in adult patients with type 1 diabetes mellitus (T1DM) or T2DM.⁷⁸⁻⁸⁰ Afrezza is intended for prandial (mealtime) insulin therapy and is intended to reach peak insulin levels in about 12–15 minutes in contrast to the 45–90 minutes for injected rapid-acting insulin and 90–150 minutes for injected regular human insulin.⁸¹ Because of this rapid peak, Afrezza insulin is considered to be an ultra-rapid-acting prandial insulin.⁸² Afrezza is a combination drug-and-device product that consists of metered doses of human insulin powder in single-use cartridges and a “whistle-sized,” disposable inhaler to deliver the insulin powder. The inhaler can be used for up to 15 days if kept clean and dry.^{80,81} Afrezza insulin is administered using the manufacturer’s Technosphere technology, a dry-powder delivery platform that reportedly mimics intra-arterial administration. The intervention consists of insulin that is encapsulated in microspheres of fumaryl diketopiperazine (a proprietary excipient) and polysorbate 80 (a common emulsifier used in food and cosmetics).^{79,83,84} Upon inhalation, the patient’s breath powers the inhaler to aerosolize the powder so that it reaches the lungs and dissolves quickly. This allows insulin to be absorbed into pulmonary arterial circulation, to achieve rapid systemic delivery.^{79,81,83} The manufacturer asserts that because Afrezza’s effect lasts about 3 hours, hyperinsulinemia occurs less often, thus lowering hypoglycemia risks and hyperinsulinemia-related weight gain.^{81,82} The manufacturer also claims that Afrezza therapy results in lower fasting glucose than can be achieved using other available mealtime insulin therapy while providing comparable overall glucose control. The manufacturer recommends a mealtime dose adjustment to be made based on “the individual’s metabolic needs, blood glucose monitoring results and glycemic control goal.”⁸⁵ The single-use cartridges contain doses of 4 units (0.35 mg of insulin) or 8 units (0.7 mg of insulin). Patients self-administer the prescribed dose inhalation at the beginning of each meal and do not administer if a meal is skipped.^{81,86}

Clinical trials: In June 2014, Afrezza’s manufacturer presented an overview of Afrezza clinical trials in its approved product labeling.⁸¹ Among 344 patients with T1DM, investigators compared mean reduction in HbA_{1c} between Afrezza plus basal insulin (n=174) and insulin aspart plus basal insulin (n=170). After 24 weeks, Afrezza plus basal insulin therapy “provided a mean reduction in HbA_{1c} that met the prespecified non-inferiority margin of 0.4%.” However, combination therapy with Afrezza provided less HbA_{1c} reduction than combination therapy with insulin aspart, and the difference reached statistical significance. The company reported that more subjects in the insulin aspart group achieved the HbA_{1c} target of 7% or lower.⁸¹

Another trial compared Afrezza to placebo, both in combination with metformin only or two or more oral antidiabetic agents, in 479 patients with T2DM. Investigators observed that after 24 weeks, the Afrezza group had a statistically significant greater reduction in HbA_{1c} than the placebo group.⁸¹

The company also reported cumulative major adverse event data associated with Afrezza therapy in 1,026 patients with T1DM and 1,991 patients with T2DM. Patients exposed to Afrezza had received Afrezza therapy for at least 5 months and up to more than 1 year. Severe hypoglycemic events occurred in 5.1% of the Afrezza group (n=177) and 1.7% of the placebo group (n=176) among patients with T2DM. Afrezza therapy was associated with reduced pulmonary function that occurred during the first 3 months of therapy and persisted over 2 years. Trials lasted up to 2 years and excluded patients with chronic lung disease. Patients treated with Afrezza had a 40 mL (95% CI, -80 to -1) greater decline from baseline in a measure of lung capacity, forced expiratory volume in 1 second (FEV₁), than did patients treated with competing antidiabetes therapies. A 15% or larger decline in FEV₁ occurred in 6% of Afrezza-treated subjects compared with 3% of subjects who received competing therapies.⁸¹

Manufacturer and regulatory status: MannKind Corp. (Valencia, CA) in collaboration with Sanofi (Paris, France) developed Afrezza. In June 2014, FDA approved Afrezza for improving glycemic control in adults with diabetes mellitus.^{81,87} FDA classifies inhaled insulin delivery systems as combination products (i.e., drug-device) and has adopted Good Manufacturing Practice guidelines that require sterile production of inhalation products and devices used to deliver them.⁸⁸ In February 2015, the companies announced a commercial rollout of prescription Afrezza to U.S. retail pharmacies.⁸⁰

FDA required a Risk Evaluation and Mitigation Strategy (REMS) for Afrezza approval, informing prescribers about potential associated risks including the serious risk of acute bronchospasm.⁸⁷ FDA advises that Afrezza should not be used in patients with chronic lung disease, such as asthma or chronic obstructive pulmonary disease, because of this risk. Thus, candidates should undergo pulmonary testing (spirometry [FEV₁]) to screen for respiratory conditions that would contraindicate use of Afrezza, as well as periodic followup spirometry to identify potential long-term respiratory problems.^{81,89} The most common adverse reactions associated with Afrezza in clinical trials were hypoglycemia, cough, and throat pain or irritation. As part of the approval, the companies agreed to several postmarketing requirements, including a study to assess safety and efficacy in pediatric patients and a trial to evaluate long-term cardiovascular and pulmonary risks. Also, two pharmacokinetic-pharmacodynamic studies will be initiated to characterize dose response and determine within-person variability.⁸⁷

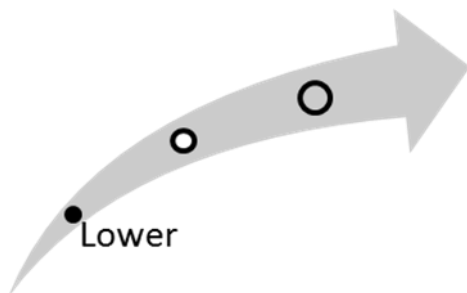
Diffusion and Cost: Although FDA approved Afrezza in June 2014, the manufacturer did not begin distributing the product to U.S. retail pharmacies until February 2015.⁸⁰ As of October 2015, Afrezza was just beginning to be listed in formularies of third-party payers, a process that can take 6 to 12 months after launch of a new drug/device combination.⁹⁰ Seeking Alpha reported that Afrezza can be found in tier 4 in state Medicare Part D prescription drug plan formularies, which is a tier where higher cost brand name drugs are listed when covered. Afrezza is also listed as a tier 5 drug in some state Medicare drug plan formularies, which is the highest pricing tier for specialty pharmaceuticals.⁹⁰

MannKind has reported \$17.1 million in Afrezza sales for the period January through September 2015; however, the company also reported overall net losses averaging about \$30 million per quarter for the same reporting period.⁹¹⁻⁹³ Thus, MannKind's long-term viability might be doubtful. To raise needed capital, MannKind reportedly planned to sell additional company shares on the Tel Aviv Stock Exchange.⁹⁴ As of December 2015, Afrezza reportedly cost from about \$230 for a 90-cartridge kit at the 4-unit dose level to about \$310 for a kit containing 30 cartridges of 4 units each and 60 cartridges of 8 units each, at U.S. retail pharmacies.⁹⁵

Clinical Pathway at Point of This Intervention

T2DM typically occurs in middle age or later, although incidence in a younger population has been growing as a result of the obesity epidemic. Initial treatment includes dietary modification, exercise, and self-monitoring of blood glucose. First-line drug therapies include biguanides, sulfonylureas, alpha-glucosidase inhibitors, insulin sensitizers, insulin secretagogues, and DPP-4 inhibitors. Some patients require combination drug therapy of agents with different mechanisms of action for additive therapeutic effects and better glycemic control. Despite the availability of oral antidiabetes drugs, many patients do not achieve treatment goals and require additional therapy with an injected antidiabetes agent: subcutaneous insulin or a GLP-1 agonist.¹ Afrezza is intended for prandial (mealtime) insulin therapy and is intended to reach peak insulin levels in about 12–15 minutes in contrast to the 45–90 minutes for injected rapid-acting insulin and 90–150 minutes for injected regular human insulin.⁸¹

Figure 3. Overall high-impact potential: ultra-rapid-acting inhaled insulin (Technosphere insulin inhalation system with Afrezza) for treating diabetes that requires insulin



Overall, experts anticipated good acceptance for inhaled insulin from physicians and patients. Some experts thought that although some clinical data suggest inhaled insulin might not always be as effective at glycemic control as injectable insulin, the convenience and improved comfort could improve outcomes by increasing adherence to insulin therapy. Experts noted that inhaled insulin represents only one component of a multifaceted treatment regimen for most patients with diabetes. Based on this input, our overall assessment is that this intervention is in the lower end of the high-impact-potential range.

Results and Discussion

Six experts, with clinical, research, and health systems backgrounds, provided perspectives on this technology.⁹⁶⁻¹⁰¹ We have organized the following discussion of expert comments by the parameters on which they commented.

Unmet need and health outcomes: Overall, experts agreed on the need for new treatment options for patients with T2DM to improve adherence to recommended therapy and success at attaining treatment goals. One health systems expert noted, “Historically, patients do not like to self inject due to the pain, inconvenience, and social stigma of injecting a medication. Many insulin products require refrigeration, adding to the inconvenience, especially while traveling or eating out.”⁹⁹ Likewise, a clinical expert stated, “Difficulty with adherence to multiple injections on a daily basis contributes to poor diabetes control. Therefore, any agent that decreases pain and inconvenience and other side effects of injectable insulin should improve adherence and thereby, diabetes control.”¹⁰⁰ Another clinical expert noted, “Inadequate glycemic control is a major problem in patients with type 1 or type 2 diabetes. Long-acting insulin injection improves baseline glucose; however, the control of meal related (prandial) glucose with injectable insulin is often suboptimal. Poorly controlled prandial glucose levels worsen HbA1C in the longterm, predisposing to vascular

complications. Afrezza has potential to improve prandial glucose levels due to its rapid onset of action.”⁹⁶ Although inhaled insulin represents only one component of the complete therapeutic regimen, most experts thought it has strong potential to improve outcomes for meal-time insulin therapy. Several experts noted that although limited available data suggest that rapid-acting injectable prandial insulin might work better than inhaled insulin, inhaled insulin might improve outcomes by improving compliance because more patients might find it less painful and more convenient to take inhaled insulin.^{96,98-101} One clinical expert stated, “Afrezza decreases prandial glucose levels and lowers glycated hemoglobin, and thus would be expected to decrease the incidence of diseases associated with poorly controlled diabetes. The effect of Afrezza on HbA1c is less than for aspart insulin, a rapidly acting injectable insulin.”⁹⁶ A research expert noted, “Availability of an insulin formulation that could more closely mimic pancreatic action and control rises in postprandial blood glucose is very important.”⁹⁸ One clinical expert who cited the intervention’s potential to improve patient health also pointed to the need for additional research to more clearly define inhaled insulin’s safety and efficacy. This clinical expert stated, “Observational data suggest potential side effects, such as a decrease in pulmonary function test parameters such as FEV1. While the FDA mandated risk evaluation and mitigation strategy (REMS) assessment is a step in the right direction, I do feel that a randomized controlled study to compare inhaled versus subcutaneous insulin is warranted.”¹⁰⁰

Acceptance and adoption: All experts anticipated good acceptance from physicians with some caveats. Patient acceptance would be somewhat higher than physician acceptance, thought the experts. One research expert noted, “Specialists caring for patients with T1DM are interested in inhaled insulin as an improved way to control rises in postmeal blood glucose.”⁹⁸ A clinical expert noted, “Given the convenience factor, I do believe that Afrezza will be widely prescribed by physicians. However, if insurance companies do not cover the medication, then the medication is less likely to be widely adopted.”¹⁰⁰ Another clinical expert opined, “The device is small and easy to operate, and is likely to be accepted by clinicians compared to frequent injections. However, clinicians may be concerned about the pre-screening and monitoring requirements.”⁹⁶ A research expert noted, “Clinicians would be concerned about imprecise dosing and patients making dosing mistakes with a new device.”⁹⁷ All experts thought that patients without pulmonary conditions would prefer inhaled insulin to multiple injections for mealtime insulin therapy. One research expert stated, “Patients would love the convenience.”⁹⁷

Health care delivery infrastructure and patient management: Experts generally expected that inhaled insulin would cause only small disruptions to health care delivery infrastructure because the therapy is self administered, although patients would require preliminary respiratory screening to determine their suitability and monitoring of pulmonary function over time. One health systems expert and a research expert opined that to the extent that glycemic control is improved, the future burden on health care infrastructure from treatment of secondary complications of diabetes might be reduced.^{99,101} Experts also anticipated a small change to the way that patients are managed. One clinical expert stated, “There will be a learning curve with the patients learning how to use their medication. This may require extra physician or nurse visits for patients to learn how to use their medication.”¹⁰⁰

Health disparities: Experts generally thought that inhaled insulin, which is easier to administer than injections, has potential to reduce health disparities in less-affluent populations, which are heavily affected by diabetes, provided that insurance coverage is available for this more costly intervention.⁹⁶⁻¹⁰¹ However, most experts also thought that inhaled insulin could increase disparities somewhat if it is not reimbursed by insurers and its cost is unattainable by many patients. One clinical expert noted, “However, given that there is a reasonable alternative (subcutaneous insulin)

that is covered under most insurance plans, health outcomes overall should not decline in patients who cannot afford the inhaled insulin.”¹⁰⁰

Diabetic Macular Edema Intervention

Fluocinolone Acetonide Implant (Iluvien) for Treatment of Diabetic Macular Edema

Unmet need: The standard treatment for diabetic macular edema (DME) is laser photocoagulation to halt vision loss, but this treatment cannot reverse vision loss that has already occurred. Further, vision loss continues to progress in some patients despite treatment.¹⁰²⁻¹⁰⁴ Laser photocoagulation used in treatment may also be associated with a small increased risk of loss of peripheral, night, or color vision.¹⁰²

Recently, intravitreal injection has become a common treatment for DME. One such injected agent is ranibizumab (Lucentis®), which FDA approved in 2012 for treating DME; it purportedly functions as an antiangiogenic agent. Additionally, because inflammation is thought to play a role in DME, off-label corticosteroid injections have been used by some retinal physicians to treat DME. Both anti-angiogenic and corticosteroid treatments require ongoing treatment involving multiple intravitreal injections per year for effective treatment.^{105,106} Thus, interest exists in developing more convenient and safer intravitreal therapies for DME.

Intervention: Iluvien® is an intravitreal insert intended for sustained release of the corticosteroid fluocinolone acetonide over three years for treating DME.¹⁰⁷ The insert consists of 190 mcg of the drug in a tiny, cylindrical, polyimide tube designed to provide sustained drug release into the eye. The insert is delivered by intravitreal injection to the back of the eye with a 25-gauge needle, a needle size that purportedly allows natural physiologic sealing of the injection site. Iluvien is designed to have a therapeutic effect for up to 36 months through stable, long-term release of fluocinolone acetonide into the eye.^{107,108}

Clinical trials with Iluvien demonstrated that patients with persistent DME responded well to Iluvien treatment despite poor responses to other treatments and that patients who had had DME for 3 years or longer responded better to treatment than those who had had DME for a shorter period.¹⁰⁹ The exact mechanism for this improved visual acuity after treatment in patients with longer-duration DME is not known. Investigators hypothesize that chronic edema may exacerbate the inflammation that occurs in DME and that corticosteroids exert a therapeutic effect by modulating vascular permeability via several mechanisms including inflammatory cell inhibition, inflammatory cytokine downregulation, and stabilization of cell membranes and tight junctions.^{105,109}

Clinical trials: In November 2015 at the American Academy of Ophthalmology meeting, the manufacturer reported that Iluvien treatment slowed progression of diabetic retinopathy compared with sham treatment in the FAME™ Study. The FAME Study consisted of 2 phase III pivotal trials that assessed the product's safety and efficacy over 3 years. Patients received a mean of 1.3 injected implants over the study duration. At 3-year followup, 17% of Iluvien-treated eyes showed progression of diabetic retinopathy and 31% of sham-treated eyes showed disease progression ($p < 0.001$). Disease progression was defined as the need for additional (i.e., post-trial-intervention) treatment of progressive diabetic retinopathy by pan-retinal photocoagulation or vitrectomy, based on analysis of fundus photographs that were graded by a masked, certified reading center.¹¹⁰

Manufacturer and regulatory status: pSivida Corp. (Watertown, MA) developed the sustained-release, drug-delivery technology and licensed it to Alimera Sciences, Inc. (Alpharetta, GA).¹¹¹ In September 2014, FDA approved Iluvien for treating DME in patients “who have been previously treated with a course of corticosteroids and did not have a clinically significant rise in intraocular pressure.”¹¹² Iluvien is also commercially available in the European Union for treating “DME considered insufficiently responsive to available therapies.”^{113,114}

Diffusion: The drug likely competes with laser photocoagulation and off-label corticosteroid injections for DME;^{105,106} vision loss may continue to progress in some patients despite those treatments.¹⁰²⁻¹⁰⁴ Fluocinolone acetonide could complement laser therapy and might be potentially

more convenient and safer than corticosteroid therapy because it would not require ongoing intravitreal steroid injections; thus, patients might find it a more appealing option.

In the United States, the Iluvien implant costs about \$8,800, not including the costs of implantation and followup.¹¹⁴ Associated implantation costs have not been widely reported since the manufacturer announced that the first products were shipped in late February 2015, after FDA approval in September 2014.¹¹¹ In the United Kingdom, the Iluvien implant costs an estimated £5,500, plus an additional £381 for the implantation procedure and another £240 for followup visits.^{115,116} At December 2015 exchange rates, estimated costs would be \$8,370 for the implant, \$580 for device implantation, and \$365 for patient followup.¹¹⁷ In November 2015, the manufacturer reported, “Iluvien continued to see growing demand” in the United States, although no individual sales figures were announced. The company also announced that it anticipated increased Iluvien sales because the product has been assigned a “J-code” for billing and reimbursement under CMS’ Healthcare Common Procedure Coding System (HCPCS) that will become effective in 2016. J-codes apply to injectable drugs that usually cannot be self-administered.¹¹⁸

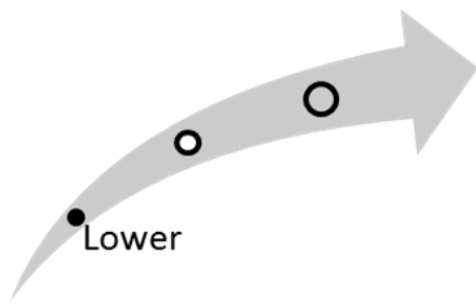
The fluocinolone acetonide implant likely also competes with ranibizumab, a vascular endothelial growth factor (VEGF) inhibitor approved for treating DME with monthly intravitreal injections.¹¹⁹ As of December 2015, ranibizumab reportedly cost \$1,936 per dose.¹²⁰

Additional DME treatments under development include other corticosteroid medications and anti-VEGF agents. Ozurdex[®] (formerly Posurdex) is a biodegradable intravitreal implant that releases low doses of the corticosteroid dexamethasone over 4 months.^{121,122} FDA has approved the drug for treating DME, uveitis, and other ocular disorders.¹²³ Bevacizumab (Avastin[®]) and pegaptanib (Macugen[®]) are anti-VEGF (antiangiogenic) drugs typically used in cancer treatment and age-related macular degeneration; in clinical trials, researchers are testing the efficacy of small doses for treating DME.¹²⁴ In one recently completed phase IV study, researchers studied the efficacy of combining Ozurdex with bevacizumab for treating DME.¹²⁵ Bevacizumab is reportedly used widely for off-label treatment of ophthalmic conditions, including DME, as a significantly less-expensive alternative to ranibizumab.¹²⁶⁻¹²⁹ However, some researchers report that intravitreal injections of bevacizumab are associated with a significantly higher rate of serious adverse events (because of the dose-preparation requirements for ophthalmic administration), which could pose an additional cost burden to treat. In one Canadian retrospective study, subjects who received bevacizumab for ophthalmic indications were 12 times as likely to develop severe intraocular inflammation after each injection as were patients who received ranibizumab injections.¹³⁰

Clinical Pathway at Point of This Intervention

All patients with a diagnosis of diabetes mellitus are at risk of developing DME. A patient who presents with symptoms suggestive of DME undergoes a history and physical examination pertaining to diabetes history, vision and eye-disease history, and other risk factors (i.e., older age, poor glucose control, pregnancy, hypertension, and increased lipid levels).¹³¹ Using a high-magnification ophthalmoscope, the ophthalmologist can identify the retinal thickening that indicates macular edema. Yellow exudates and poor visual acuity may also be detected. DME treatment focuses on glycemic control, optimal blood pressure control, and macular focal/grid laser photocoagulation. Standard therapy has been laser photocoagulation and intravitreal injections of ranibizumab, off-label bevacizumab, or corticosteroids.¹³¹ Use of Iluvien would replace frequent intravitreal injections for up to 3 years, according to the manufacturer.

Figure 4. Overall high-impact potential: fluocinolone acetonide implant (Iluvien) for treatment of diabetic macular edema



The rising incidence of diabetes raises the risk of vision problems including DME and creates a large unmet need for more effective DME treatments, the experts agreed. They opined that this implant has the potential to improve health outcomes by increasing medication adherence and reducing the frequency of required clinic visits. However, several experts expressed concerns about potential adverse events, including a risk of cataracts and glaucoma. Clinician acceptance is likely to be moderated by the potential for adverse events, experts thought. Patients would be more likely to accept this intervention for its convenience, although they would also weigh risk of adverse events in consultation with their physicians. Based on this input, our overall assessment is that this intervention is in the lower end of the high-impact-potential range.

Results and Discussion of Comments

Seven experts, with clinical, research, and health systems backgrounds, provided perspectives on the fluocinolone acetonide implant.¹³²⁻¹³⁸ We have organized the following discussion of expert comments according to the parameters on which they commented.

Unmet need and health outcomes: Most experts concluded that an unmet need exists, based on the rising incidence of diabetes, coupled with the varied effectiveness of and need for multiple applications of available therapies for DME. However, one health systems expert saw little unmet need, because of the availability of competing treatments for DME.¹³² Experts were split over the intervention's potential to improve patient health. Two research experts and a health systems expert thought that Iluvien offers little added health benefit compared with repeated intravitreal steroid injections and that few available data compared Iluvien to alternate therapies.^{132,136,137} However, three clinical experts and a research expert believe that Iluvien's greatest benefit is its ability to provide long-term administration of steroids, which could improve treatment consistency and alleviate issues of treatment compliance or regular access to treatment associated with repeated steroid injections. One research expert noted, "Even if Iluvien is proven to be as effective as current drug treatment, its significance lies in its ability to be long-lasting (reportedly up to as long as 3 years). The longest implant prior to Iluvien was a dexamethasone implant that lasted about 4 months. Thus in terms of patient compliance, this is a significant advantage."¹³³ Another clinical expert stated, "There is definite, real potential to help in visual outcomes of patients with diabetic macular edema. We know steroids help improve vision, so longer-lasting steroids would help longer term as the preliminary data show. However the rate of development of glaucoma requiring surgery is not to be taken lightly.... Choice of who are the best candidates for the steroid implant may require some level of screening for glaucoma to avoid this complication."¹³⁵

Acceptance and adoption: Generally, experts anticipated moderate adoption of Iluvien by clinicians and patients, with patient acceptance trending somewhat higher. Experts thought that physicians and patients would weigh the convenience of a single injection lasting 3 years against the risk of cataracts and glaucoma. One health systems expert thought that the availability and

amount of reimbursement for the Iluvien procedure compared with coverage of multiple steroid injections would greatly influence physician acceptance.¹³² This expert also believes that costs would likely influence patient acceptance, stating, “Patients would most likely prefer this intervention as compared to the current intervention that requires much more frequent intraocular injections. I feel the deciding factor for most patients would be their out of pocket expenses.”¹³² One clinical expert noted, “Patients will like the idea of improved vision and reducing need for multiple injections. There is already an acceptance of intravitreal injections for retinal conditions, so I don’t think that there will be any problem accepting this if doctor-recommended.”¹³⁵ However, a research expert stated, “Initially, patients are likely to accept this treatment because of the single injection, but the risk of cataracts and glaucoma is high, which should temper their enthusiasm.”¹³³

Experts generally thought that although Iluvien may be less costly than injections of anti-angiogenesis (anti-VEGF) drugs ranibizumab or pegaptanib, the risk of adverse events, such as cataracts or glaucoma, may reduce any potential savings. One research expert noted, “When compared with intra-vitreous injections of anti-VEGF drugs over a 2-3 year period, the projected cost of \$8,000 is significantly lower than ranibizumab (\$20,000-40,000/year) or Macugen [pegaptanib] (\$16,000-18,000/2 years). However, cost of treating adverse effects of cataract/glaucoma has not been taken into consideration, nor the loss of work days and disability due to these effects.”¹³³

Health care delivery infrastructure and patient management: Overall, experts thought that use of Iluvien would create few disruptions to health care infrastructure or patient management procedures in the short term. Implants would be injected in the same facilities where multiple steroid injections are administered now. The number of injections and office visits could be greatly reduced if the treatment lasts up to 3 years. One research expert stated, “Facilities performing photocoagulation procedures would probably do fewer of those procedures, which would be offset by an increase in implantation of Iluvien inserts.”¹³⁸ However, experts also thought the risk of glaucoma and cataracts could increase health care use for the subgroup of patients in which they occur. One research expert noted, “Since Iluvien requires a single intra-vitreous injection (which is currently the mode of treatment with other drugs), no changes in physical resources should be anticipated. However if fewer visits are anticipated compared to available treatments, then number of staff might need to be reduced.”¹³³ Another clinical expert stated, “The amount of care that needs to be delivered has the potential to be higher due to complications with the risk of surgical intervention for glaucoma surgery, which includes more expenses for additional consultation for glaucoma diagnosis and decisions for surgery and possible costs to hospitals for indigent patients who may suffer from complications.”¹³⁵

Health disparities: Experts rated Iluvien’s potential effect on disparities from small to moderate to large. A health systems expert stated, “Due to its high cost and its minimal acceptance by insurers, I do not feel this intervention will aid in the decrease of any health disparities.”¹³² A clinical expert noted, “Diabetic macular edema is more common in racial/ethnic groups with a higher prevalence of diabetes, i.e., Hispanic-, African-, Native Americans. Improved diabetic macular edema outcomes with Iluvien therapy is likely to decrease the incidence of blindness in these groups.”¹³⁴ Another clinical expert stated, “Because the complication rate for glaucoma surgical requirement is so high, this possible complication may not be well communicated or understood by certain groups of patients who have already been established to have higher risk for developing glaucoma (blacks/Hispanics) or poor followup in established glaucoma or glaucoma suspicion (low economic status and low literacy level).”¹³⁵ A research expert stated, “Iluvien is likely to have some effect on health disparities. The investigators report the cost of Iluvien to be \$8,000, which is significantly cheaper than Retisert [a fluocinolone acetonide intravitreal implant]. It is still a costly treatment and may be an option for patients with high economic status and/or those whose insurance coverage covers this treatment modality. The single injection will likely be an

advantage in terms of patient compliance, fewer days missed from work when compared with multiple injections of other drugs. Thus, this may even out the disparity for low economic status/low literacy patients. However, the higher incidence of adverse effects (cataract and glaucoma) may have a counter effect.”¹³³

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